Adverse Childhood Experiences and the Risk of Premature Mortality

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Background: Strong, graded relationships between exposure to childhood traumatic stressors and numerous negative health behaviors and outcomes, healthcare utilization, and overall health status inspired the question of whether these adverse childhood experiences (ACEs) are associated with premature death during adulthood.

Purpose: This study aims to determine whether ACEs are associated with an increased risk of premature death during adulthood.

Methods: Baseline survey data on health behaviors, health status, and exposure to ACEs were collected from 17,337 adults aged >18 years during 1995–1997. The ACEs included abuse (emotional, physical, sexual); witnessing domestic violence; parental separation or divorce; and growing up in a household where members were mentally ill, substance abusers, or sent to prison. The ACE score (an integer count of the eight categories of ACEs) was used as a measure of cumulative exposure to traumatic stress during childhood. Deaths were identified during follow-up assessments (between baseline appointment date and December 31, 2006) using mortality records obtained from a search of the National Death Index. Expected years of life lost (YLL) and years of potential life lost (YPLL) were computed using standard methods. The relative risk of death from all causes at age ≤65 years and at age ≤75 years was estimated across the number of categories of ACEs using multivariable-adjusted Cox proportional hazards regression. Analysis was conducted during January–February 2009.

Results: Overall, 1539 people died during follow-up; the crude death rate was 91.0 per 1000; the age-adjusted rate was 54.7 per 1000. People with six or more ACEs died nearly 20 years earlier on average than those without ACEs (60.6 years, 95% CI=56.2, 65.1, vs 79.1 years, 95% CI=78.4, 79.9). Average YLL per death was nearly three times greater among people with six or more ACEs (25.2 years) than those without ACEs (9.2 years). Roughly one third (n=526) of those who died during follow-up were aged ≤75 years at the time of death, accounting for 4792 YPLL. After multivariable adjustment, adults with six or more ACEs were 1.7 (95% CI=1.06, 2.83) times more likely to die when aged ≤75 years and 2.4 (95% CI=1.30, 4.39) times more likely to die when aged ≤65 years.

Conclusions: ACEs are associated with an increased risk of premature death, although a graded increase in the risk of premature death was not observed across the number of categories of ACEs. The increase in risk was only partly explained by documented ACE-related health and social problems, suggesting other possible mechanisms by which ACEs may contribute to premature death.
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Introduction

The Adverse Childhood Experiences (ACE) Study, a collaborative effort between Kaiser Permanente (San Diego CA) and the CDC (Atlanta GA), was designed to examine the long-term relationship between ACEs and a variety of health behaviors and health outcomes in adulthood.[1] The ACE Study proposes that stressful or traumatic childhood experiences have negative neurodevelopmental impacts that lead through life pathways and increase the risk of a variety of behavioral, health, and social problems. The ACE pyramid is used to depict this concept (www.cdc.gov/nccdphp/ace/pyramid.htm). The seminal paper of the ACE Study[1] described associations between the number of categories of ACEs and prevalent cases of disease that

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underlie many of the leading causes of death in the U.S. Relationships have since been reported between ACEs and numerous health-risk behaviors, health outcomes, healthcare utilization, and health status.[2] A case–control study[3] conducted in Washington State described an increased risk of death prior to age 18 years among substantiated cases of child abuse relative to a comparison population, whereas a study of substantiated cases of abuse and matched neighborhood controls reported no association between abuse and mortality in young adulthood.[4] On the basis of this evidence, a prospective cohort study of 16,908 adults was initiated to assess the relationship between the cumulative effects of ACEs and premature mortality.

Methods

The ACE Study is based at Kaiser Permanente's San Diego Health Appraisal Clinic, a primary care clinic where more than 50,000 adult members of the Kaiser Permanente HMO receive an annual, standardized, biopsychosocial medical examination.[5] Each member who visits the Health Appraisal Clinic completes a standardized medical questionnaire.[1] The medical history is completed by a healthcare provider who also performs a general physical exam and reviews laboratory test results with the patient.[1] Appointments for most members are obtained by self-referral, with 20% referred by their healthcare provider.[1] A review of continuously enrolled (between 1992 and 1995) Kaiser Permanente members aged ≥25 years in San Diego revealed that 81% of those members had been evaluated at the Health Appraisal Clinic.[1]

All health plan members who completed standardized medical exams at the clinic between August and November 1995; between January and March 1996 (Wave I, n=13,494); and between April and October 1997 (Wave II, n=13,330) were eligible to participate in the baseline ACE Study.[6] Within 2 weeks after a member's visit to the clinic, a study questionnaire was mailed asking questions about health behaviors and ACEs. The overall response rate to the mailed questionnaire was 68% (18,175/26,824).[6] The ACE questionnaire nonrespondents were generally younger and more often male, nonwhite, and less highly educated than those who responded.[7]

Definition of ACEs

Adverse childhood experiences include childhood emotional, physical, or sexual abuse and household dysfunction. The categories are verbal abuse, physical abuse, contact sexual abuse, a battered mother, household substance abuse, household mental illness, incarcerated household members, and parental separation or divorce (Table 1). The experiences studied were chosen based on prior research that has shown them to have significant negative health or social implications, and because substantial efforts are being made in the public and private sector to reduce the frequency of occurrence. A complete description of ACEs is provided elsewhere.[5,8]

Exposure to ACEs is captured in the ACE score. The ACE score is a simple summation (integer count) of exposure to each of eight categories of adverse experiences during the respondents' first 18 years of life. Exposure to any ACE category counts as one point on the score. The statistical characteristics and validity of the ACE score and test–retest reliability of the questions have been published elsewhere.[9,10] Analyses were completed using both a continuous ACE score variable and a six-level categoric ACE score variable (0, 1, 2, 3, 4, or 5, and ≥6 ACEs), with 0 ACEs serving as the referent category.

Follow-Up Data

To ascertain the vital status of cohort members through December 31, 2006, ACE Study baseline data were merged with mortality data from the National Death Index (NDI), shown to capture 93%–98% of all deaths in the U.S.[11–13] Linkage of ACE Study participants with NDI records followed standardized procedures used by the National Center for Health Statistics.[14–16] Briefly, 6795 study participants were matched to the NDI by social security number, first and last names, middle initial, gender, birth date, and state of residence. Eligible participants with a "true" NDI record match were assumed to be dead (n=1539), and those with no NDI record match or an NDI record match considered to be a "false" match were assumed to be alive.[14–16] A description of the merging process is provided in Appendix A, available online at www.ajpm-online.net.

Follow-up time was calculated as the difference between the ACE Study baseline interview date and the last known date alive for study participants listed as decedents in the NDI and as the difference between the interview date and December 31, 2006, for those assumed to be alive (n=15,369). A total of 429 observations were excluded from follow-up because the baseline appointment date occurred outside of a period of enrollment in the Kaiser health plan or within 120 days of a period of enrollment; therefore these people were not enrolled in the Kaiser health plan at baseline and thus were not eligible for study follow-up. The 120-day rule was incorporated to account for possible coverage by the health insurance plan under coverage continuation provided by the Consolidated Omnibus Budget Reconciliation Act of 1985. There were no deaths identified among these observations. People excluded from follow-up were slightly younger and more likely to be nonwhite, unmarried, or report financial problems than those who constituted the follow-up cohort. Small differences were observed by gender or education level. No meaningful difference was observed in the ACE score distribution between the two groups.

Measures of Premature Mortality

Crude and age-adjusted death rates are dominated by the underlying disease processes of older adults and thus do not reflect the burden of deaths occurring at younger ages, which are often preventable and have the potential to affect the available workforce. Thus, measures of premature mortality attempt to give more importance to the deaths of younger adults than to those of older adults. Relationships between the number of categories of ACEs and several measures of premature mortality were studied.

Standard expected years of life lost (YLL). The YLL measure, developed by the Global Burden of Disease (GBD) Study,[17] is based on comparing the average age of death to

Table 1. Definition and prevalence of ACEs occurring during the first 18 years of life, by age

	Aged <65 years, % (*n*=11,749)	Aged ≥65 years, % (*n*=5588)
CHILDHOOD ABUSE		
Emotional[a]	13.0	5.4
Did a parent or other adult in the household . . .		
(1) Often or very often swear at you, insult you, or put you down?		
(2) Sometimes, often, or very often act in a way that made you afraid that you might be physically hurt?		
Physical	32.3	19.9
Did a parent or other adult in the household . . .		
(1) Often or very often push, grab, slap, or throw something at you?		
(2) Often or very often hit you so hard that you had marks or were injured?		
Sexual	22.5	17.0
Did an adult or person at least 5 years older ever . . .		
(1) Touch or fondle you in a sexual way?		
(2) Have you touch their body in a sexual way?		
(3) Attempt oral, anal, or vaginal intercourse with you?		
(4) Actually have oral, anal, or vaginal intercourse with you?		
HOUSEHOLD DYSFUNCTION		
Substance abuse	32.3	15.4
(1) Live with anyone who was a problem drinker or alcoholic?		
(2) Live with anyone who used street drugs?		
Mental illness	22.5	12.9
(1) Was a household member depressed or mentally ill?		
(2) Did a household member attempt suicide?		
Mother treated violently	14.9	8.1
Was your mother (or stepmother) . . .		
(1) Sometimes, often, or very often pushed, grabbed, slapped, or had something thrown at her?		
(2) Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard?		
(3) Ever repeatedly hit over at least a few minutes?		
(4) Ever threatened with or hurt by a knife or gun?		
Incarcerated household member	5.6	2.7
(1) Did a household member go to prison?		
Parental separation or divorce	26.1	17.3
(1) Were your parents ever separated or divorced?		
Categories of ACEs (#)		
0	30.9	47.0
1	25.3	27.6
2	17.0	13.7
3	11.0	6.4
4 or 5	12.1	4.8
6, 7, or 8	3.7	0.6

[a]Respondents were defined as exposed to a category if they responded yes to one or more of the questions in that category.
ACEs, adverse childhood experiences

an external standard life expectancy curve. For groups with life expectancies that exceed these standards, a health gap for each death remains because the model life table is used to define the loss function and thus captures lost years of life for a death at each age.[18] Thus, the YLL measures lost life-years for every death. The YLL measurement is in contrast to approaches based on normative population survival that do not measure deaths after a designated cut-off age. In keeping with the methods used by the GBD Study, YLL, average YLL, and age-standardized YLL (ASYLL) were computed using established methods.[19] The Coale and Demeny[20] model life tables were used with life expectancy at birth, assumed to be 82.5 years for women and 80 years for men.

Years of potential life lost (YPLL). YPLL measures the number of years lost for an individual who fails to live an expected number of years based on a specified life expectancy.[21] YPLL is calculated by subtracting age at death from a specified standard death age (e.g., 65 or 75 years) for each decedent and then summing these differences across individuals for a total YPLL. For example, if the selected age limit is 70 years and a person dies at age 30 years, then that person is considered to have lost 40 years of potential life.

Relative risk of death from all causes at age ≤75 years. Multivariable-adjusted Cox proportional hazards regression was used to estimate, by means of the hazard rate ratio, the risk ratio for death from all causes at age ≤75 years associated with an ACE score of 1, 2, 3, 4, or 5, and ≥6 compared to an ACE score of 0. Models were repeated for death at all ages and ages <65 years. Multivariable-adjusted models controlled for age, gender, race/ethnicity, education, marital status, and current problems with finances. Relationships between ACEs and premature death were also examined after the addition of health and social problems previously shown to be associated with ACEs (i.e., possible causal intermediates).

Statistical Analysis

Analyses were conducted using SAS version 9.1.3. Mortality rates per 1000 person-years were computed by dividing the number of deaths by the person-time experience. Mortality rates were age-standardized using the 2000 Census population for California. The appropriateness of the proportional hazard assumption was assessed for the variables in the final model; without exception, all covariates in the final model satisfied the proportional hazard assumption. The ACE Study has been approved by the IRBs of the respective institutions.

Results

Responses to the eight individual ACE components varied by age such that a higher proportion of participants aged <65 years reported ACEs and had higher ACE scores than respondents aged ≥65 years at baseline (Table 1). However, the overall prevalence of ACEs was high, with one or more ACEs reported by 69.1% of participants aged <65 years and by 53.0% of those aged ≥65 years.

The frequency of deaths from all causes and mortality rates by selected study participant characteristics are shown for men and women in Table 2. Of the 16,908 study participants in the follow-up study (followed for 131,681 person-years; M=7.8 years, SE=0.03), 1539 (followed for 8255 person-years; M=5.4 years, SE=0.07) died between the baseline appointment date and December 31, 2006. Overall, the age-adjusted rate was 54.7 per 1000 population (crude, 91.0 per 1000). As expected, people who died were older and more often men, nonwhite, and unmarried; had a lower education level; and reported current financial problems more often than those who survived follow-up (or were censored).

The five leading causes of death accounted for about 90% of all deaths among study participants. In rank order according to the number of deaths, the leading causes were diseases of the circulatory system (heart disease and stroke; n=538 deaths; crude death rate=31.8 per 1000 population; age-adjusted rate=19.2 per 1000 population); malignant neoplasms (cancer; n=517 deaths; crude death rate=30.6 per 1000 population; age-adjusted rate=16.4); diseases of the nervous system and sense organs (n=140 deaths; crude death rate=8.3 per 1000 population; age-adjusted rate=5.1 per 1000 population); diseases of the respiratory system (n=137 deaths; crude death rate=8.1 per 1000 population; age-adjusted rate=4.9 per 1000 population); and diseases of the digestive system (n=50 deaths; crude death rate=3.0 per 1000 population; age-adjusted rate=1.8 per 1000 population).

Table 2. Frequency of deaths from all causes and age-standardized mortality rates among ACE Study participants

		Total (N=16,908)		Women (n=9,122)		Men (n=7,786)	
	n	# of deaths	Mortality rate[a]	# of deaths	Mortality rate[a]	# of deaths	Mortality rate[a]
Overall, crude	16,908	1,539	11.7	656	9.2	883	14.7
Age-adjusted[b]		—	7.7	—	6.0	—	9.9
Age (years)							
18–34	1,611	8	0.8	2	0.3	6	1.8
35–49	4,391	59	1.7	30	1.6	29	2.0
50–64	5,410	247	5.7	106	4.6	141	6.8
65–74	3,652	514	16.6	230	14.3	284	19.1
≥75	1,844	711	52.3	288	41.9	423	62.8
Race/ethnicity[b]							
White	12,683	1,353	7.9	572	6.2	781	10.1
Black	767	48	8.4	20	5.7	28	12.4
Asian	1,875	78	6.6	39	5.0	39	8.9
Hispanic	1,218	37	5.2	14	3.6	23	8.0
Other	365	23	10.8	11	11.7	12	6.0
Education[b]							
Less than high school	1,218	203	11.9	88	41.1	115	18.9
High school graduate	2,976	408	7.8	205	6.5	203	10.1
Some college	6,056	487	7.4	206	5.9	281	9.4
College graduate	6,658	441	6.5	157	5.3	284	7.5
Married[b]							
Yes	11,758	1,053	7.1	387	5.5	666	8.3
No	5,150	486	8.3	269	6.4	217	12.3
Current problems with finances[b]							
Yes	1,967	109	12.7	56	11.1	53	17.2
No	14,941	1,430	7.4	600	5.6	830	9.9
Categories of ACE (#)[b]							
0	6,125	723	7.7	325	11.1	398	5.9
1	4,411	408	8.0	160	9.4	248	6.3
2	2,682	220	8.4	79	9.9	141	7.1
3	1,601	87	9.7	38	14.0	49	3.9
4 or 5	1,639	81	22.4	41	6.2	40	21.5
6, 7, or 8	450	20	7.3	13	8.6	7	3.4

[a]Per 1000 person-years
[b]Rate age-standardized to the 2000 Census population for California
ACEs, adverse childhood experiences

The relationship between ACEs and age-adjusted all-cause mortality rates was unclear inasmuch as a consistent pattern was not observed across the ACE scores (Table 2). After multivariable adjustment, a relationship was observed between the risk of death (at any age) from all causes and ACE scores of ≥6 (hazard ratio [HR]=1.54, 95% CI=0.98, 2.40; ref, 0 ACEs); any association between fewer categories of ACEs and the risk of death was very small, with HRs clustered around the null (ACE=1: HR=0.97 [95% CI=0.86, 1.10]; ACE=2: HR=1.05 [95% CI=0.90, 1.23]; ACE=3: HR=0.91 [95% CI=0.73, 1.14]; ACE=4 or 5: HR+1.07 [95% CI=0.85, 1.35]).

Overall, the average age at death was 77.5 (95% CI=77.0, 78.1) years. No meaningful difference in average age at death was observed between men and women or between married and unmarried people, whereas a difference was observed between whites and nonwhites as well as across education levels, with people having a high school education or less being older on average at death than those with a college education (Appendix B, available online at www.ajpm-online.net). People with six or more ACEs died nearly 20 years earlier on average than those without ACEs. Of course, comparisons of average age at death across groups are not straightforward, because the average age at death depends to a large extent on the age distribution of the underlying groups being compared.

Overall, the 1539 deaths during follow-up were associated with 15,998 YLL, with an average YLL of 10.4 years per death (Table 3). As noted above, standard expected YLL are based on comparing the age of death to standard model life tables for men and women and incorporate the mortality experience from all deaths regardless of age at death. Average YLL per death was nearly three times greater among people with six or more ACEs (25.2 years) than those without ACEs (9.2 years). To allow comparisons across groups after controlling for age, age-standardized YLL were computed and were 1.5 times greater among people with six or more ACEs than among those without ACEs (1028.8 vs 701.5 per 100,000 population). Age-standardized YLL did not increase substantially with an increase in the number of ACEs among those with fewer than six ACEs.

The frequency and age-adjusted risk of death prior to ages 65 and 75 years and the associated average years of potential life lost ($YPLL_{65}$ and $YPLL_{75}$) are shown in Table 4. Roughly 12% (n=181) of those who died during follow-up were aged ≤65 years at the time of death, accounting for a total of 1674 $YPLL_{65}$ (M=9.2 years, SE=0.68). Men lost a total of 955 $YPLL_{65}$ (M=9.3 years, SE=0.97), and women lost 719 $YPLL_{65}$ (M=9.2, SE=0.93). Similarly, about one third (n=526) of those who died during follow-up were aged ≤75 years at the time of death, accounting for a total of 4792 $YPLL_{75}$ (M=9.1 years, SE=0.41), and with a total of 2692 $YPLL_{75}$ (M=9.4 years, SE=0.57) for men and 2100 $YPLL_{75}$ (M=8.8, SE=0.58) for women. Average $YPLL_{65}$ and $YPLL_{75}$ per death were increased (although not uniformly) across ACE score categories.

Table 3. Expected YLL, average YLL, and ASYLL from all-cause mortality[a]

Categories of ACE (#)	n	# of deaths	YLL	Average YLL	ASYLL	ASYLL Ratio
0	6,125	723	6,675.6	9.2	701.5	1.00[b]
1	4,411	408	4,062.0	10.0	609.9	0.87
2	2,682	220	2,476.8	11.3	679.6	0.97
3	1,601	87	1,162.5	13.4	723.7	1.03
4 or 5	1,639	81	1,116.8	13.8	588.0	0.84
6, 7, or 8	450	20	504.0	25.2	1,028.8	1.47
Total	16,908	1,539	15,997.7	10.4	664.5	

Note: Formulas used for the computation of YLL:

- Standard expected YLL were calculated using the formula

$$YLL={}_nY_x=({}_nD_x)({}_ne^s{}_x),$$

where ${}_nD_x$ is the number of deaths within age interval x and $x+n$. The expected years of life remaining for those deaths (${}_ne^s{}_x$) was obtained using the formula

$${}_ne^s{}_x=e^s{}_x+({}_na_x-x)\frac{e^s{}_{x+n}-e^s{}_x}{(x+n)-x},$$

where ${}_na_x$ is the average age of death for the age interval, and $e^s{}_x$ and $e^s{}_{x+n}$ are life expectancies from the Coale and Demeny[20] life tables at ages x and $x+n$.

- Average YLL were calculated by dividing YLL by the corresponding number of deaths.
- ASYLL per 100,000 population were calculated according to the formula

$$ASYLL=\frac{{}_nY_x}{{}_nN_x}\times{}_nw_x,$$

where ${}_nY_x$ is the YLL for the age interval, ${}_nN_x$ is the total number of subjects in the age interval, and ${}_nw_x$ is the weight for the age interval. Age-standardized YLL were age-standardized to the 2000 Census population for California.

[a]For 1539 study participants who died between baseline and December 31, 2006

[b]People with no ACEs are the ref group for ratio comparisons.

ACEs, adverse childhood experiences; ASYLL, age-standardized YLL; YLL, years of life lost

After multivariable adjustment, adults with six or more ACEs were 1.7 times more likely to die at age ≤75 years (≥6 vs 0 ACEs: HR=1.73; 95% CI=1.06, 2.83); any association between fewer categories of ACEs and risk of premature death was again very small, with relative hazards clustered around the null. Similar results were observed for all-cause mortality at age ≤65 years (≥6 vs 0 ACEs: HR=2.39; 95% CI=1.30, 4.39).

Finally, the analysis considered whether health and social problems previously shown to be associated with ACEs accounted for relationships described above. After adding variables for prevalent disease conditions, risk factors, poor mental health, sexual and reproductive health, social problems, and prescription medication utilization (i.e., "ACE-related" conditions) into a model for premature death, risk ratios for the ACE score were attenuated toward the null, although not completely. For example, after addition of ACE-related conditions, adults with six or more ACEs were 1.2 (95%

Table 4. Frequency and risk of death prior to age 65 or to age 75 years and the associated total and average YPLL[a]

Categories of ACE (#)	n	Death prior to age 65 years				Death prior to age 75 years			
				$YPLL_{65}$				$YPLL_{75}$	
		# of deaths	Risk[b]	Total	M (SE)	# of deaths	Risk[b]	Total	M (SE)
0	6,125	61	11.0 (2.44)	501	8.2 (1.09)	203	18.9 (2.53)	1,602	7.9 (0.60)
1	4,411	39	8.4 (1.93)	326	8.4 (1.53)	140	16.6 (2.08)	1,102	7.9 (0.72)
2	2,682	35	11.1 (2.09)	318	9.1 (1.64)	75	17.3 (2.30)	830	11.1 (1.18)
3	1,601	17	11.7 (3.69)	215	12.6 (2.40)	41	18.6 (3.93)	486	11.9 (1.77)
4 or 5	1,639	15	6.2 (1.63)	144	9.6 (2.15)	49	18.2 (2.55)	440	9.0 (1.24)
6, 7, or 8	450	14	24.2 (6.48)	170	12.1 (2.52)	18	30.8 (7.29)	332	18.4 (2.59)
Total	16,908	181	10.4 (1.04)	1,674	9.2 (0.68)	526	18.3 (1.11)	4,792	9.1 (0.41)

Note: $YPLL_{65}$=65−age at death; by definition, deaths after age 65 are not considered. $YPLL_{75}$=75−age at death; by definition, deaths after age 75 are not considered.

[a]For study participants who died between baseline and December 31, 2006

[b]Age-standardized risk of death (per 1000 population); standardized to the 2000 Census population for California

ACEs, adverse childhood experiences; YPLL, years of potential life lost; $YPLL_{65}$, YPLL with death at age 65; $YPLL_{75}$, YPLL with death at age 75

CI=0.70, 1.95) times more likely to die at age ≤75 years than those without ACEs, about a 30% change in the relative hazard noted above. A similar result was observed for death at age ≤65 years.

Discussion

In this prospective cohort study, people exposed to multiple childhood traumatic stressors captured in the ACE score were at increased risk of premature death compared to people without ACEs. In contrast to prior ACE Study analyses demonstrating strong, graded relationships between the ACE score and a variety of health behaviors and health outcomes, a graded increase was not observed in the risk of premature death across the number of categories of ACEs. For nearly all measures, the analysis suggested that the burden of premature death was greatest for people with high (≥6) ACE scores, although results were constrained by a small number of cases among those exposed to high levels of ACEs. When health and social problems that may lie in the causal pathway between ACEs and premature mortality were accounted for, the apparent effects of ACEs on the risk of death at younger ages were reduced. Thus, as would be expected, the documented ACE-related conditions among participants appear to account for some, although not all, of the increased risk of premature death observed in the current study.

The observed modest associations between ACEs and all-cause mortality at any age (and associated YLL) are not unexpected for at least two reasons. First, age is inversely related to ACEs (Table 1), and the age structure of the cohort, which is composed of predominantly white, middle-class adults who are enrolled in the Kaiser health plan and who survived to the study period, is skewed toward older age groups. One third of the study sample was aged ≥65 years at baseline; 60% were aged ≥50 years at baseline. To the extent that aging represents the natural effect of time and the environment on living organisms, it makes intuitive sense that as individuals continue to age into the 7th, 8th, and 9th decades, it becomes more challenging to discern any influence of exposure to traumatic stress during childhood despite evidence suggesting that such events may become "hardwired" into an individual's biology. This is particularly true for mortality outcomes because most deaths occur among people in older age groups.

Secondly, a review of prior ACE Study results reveals that the strongest associations exist between ACEs and mental health or psychosocial-related risk behaviors and outcomes. With the exception of smoking, relationships between ACEs and the major risk factors for chronic disease (e.g., obesity, physical inactivity, hypertension, high blood cholesterol, diabetes), as well as several forms of prevalent chronic disease itself have been modest, with relatively stronger associations at the upper end of the ACE score distribution.

By extension, it is reasonable to postulate that cumulative exposure to ACEs may accelerate an individual's disease experience, putting them at increased risk for premature mortality. Although the absolute risks of death prior to age 65 or 75 years by ACE score were small, the relative risks comparing people with more than six ACEs to those without were 1.7 and 2.4, respectively.

There are several reasons to believe that these estimates of the relationship between ACEs and premature death are conservative. Some degree of selection bias is inevitable in observational research simply because not all people who are born will survive to the observation period of interest and because the population that does survive often differs from the population that does not (of course, it is not known what these differences are). If prior results from the ACE Study and similar studies are true, then it is reasonable to postulate that people who are exposed to ACEs (particularly multiple ACEs) are more likely (compared to those who are unexposed) to be aborted; die during childhood or young adulthood; be institutionalized; or be otherwise lost prior to the

initiation of the ACE Study. Thus, the association between ACEs and premature all-cause mortality would be biased downward to the extent that people surveyed at baseline differ from those who do not survive to baseline. Some caution must be exercised in making such an assertion with regard to the direction of the bias because this does not always hold for nondichotomous exposures.

The absence of a graded relationship between the ACE score and risk of premature death may not be unexpected. The finding is consistent in many ways with those of the seminal ACE Study results.[1] As noted above, previously reported relationships between ACEs and the major risk factors for chronic disease and prevalent chronic diseases, which account for more than 75% of deaths during follow-up in this cohort, were modest in the middle of the ACE score distribution. In contrast, relationships between ACEs and alcohol abuse, illicit drug use, sexual promiscuity, and suicide (which are related to causes of death that constitute a smaller fraction of total death) exhibited strong, graded relationships across the ACE score.

The study has several strengths. Mortality data were obtained prospectively from a search of the NDI and therefore are not subject to differential misclassification. Examination of the mortality data suggests that the relationship of ACEs to premature death is not limited to any specific cause of death (data not shown). Future analyses will detail relationships of ACEs to increased risk of cause-specific mortality. Also, the ACE Study incorporates multiple forms of childhood traumatic stressors. Studies that examine only one or at most two types of stressors may underestimate the burden of exposure; fail to recognize the interrelationships among different types of traumatic stressors during childhood (see Dong et al.[9]); and/or incorrectly attribute long-term consequences to single types of childhood traumatic stress[22] despite convincing evidence suggesting that exposure to multiple forms of abuse and traumatic stressors appears to influence health behaviors and outcomes through a cumulative process.

The results of this study are subject to several limitations. The frequency of ACEs may represent an underreporting of their actual occurrence given the sensitive nature of the questions. However, these estimates of the prevalence of childhood exposures are similar to estimates from nationally representative surveys[23,24] indicating that the experiences of ACE Study participants are comparable to those of the larger population of adults. For example, the ACE Study shows that 16% of the men and 25% of the women met the case definition for contact sexual abuse; a national telephone survey of adults in the U.S.[25] using similar criteria for sexual abuse estimated that 16% of men and 27% of women had been sexually abused. Of the men from the ACE Study, 30% had been physically abused as boys, which closely parallels the prevalence (31%) found in a recent population-based study of Ontario men that used questions from the same scales.[26] The similarity in estimated prevalence of these childhood exposures between the ACE Study and other population-based studies suggests that these findings are likely to be applicable in other settings.

Although mortality follow-up was available for a maximum of 10 years, statistical power was somewhat limited owing to relatively few deaths during follow-up among people exposed to multiple ACEs. Overall, the sample population under observation is a healthier group identified from the underlying source population based on their attendance at a wellness clinic. Plans for future research include continuing to repeat the NDI search and related analyses. As is the case in many observational studies, there may have been unknown or unmeasured confounding factors for which adjustment was not possible. Moreover, measurement error in the assessment or estimation of covariates and their severity may have resulted in incomplete adjustment and residual confounding. Finally, throughout this analysis, the focus was on estimation rather than significance for inference. These data are compatible with a moderate association between ACEs and premature mortality; however, this assumes that there is no bias in the data collected and that the statistical models are correct.[27]

In conclusion, exposure to ACEs is common, and their health consequences are often hidden from view by clinicians and health professionals. In the present study, people exposed to ACEs, particularly those exposed to multiple (in this study, six or more) stressors, died younger than those who were not exposed. Some of this increase in risk is explained by ACE-related health and social problems. These results, although tentative, lend further support to the collective body of evidence suggesting that childhood traumatic stressors represent a common pathway to a variety of long-term behavioral, health, and social problems. Additional studies of the prevalence of ACEs in other populations and examination of relationships with health and social problems are needed.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC or the authors' affiliated institutions.

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Appendix

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amepre.2009.06.021.